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# A short and efficient synthetic protocol for the synthesis of 5-substituted-4,6-dioxo-pyrrolo[2,3-*d*]pyrimidines

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ABSTRACT

A short and efficient synthesis for 5-substituted-4,6-dioxo-pyrrolo[2,3-*d*]pyrimidines has been developed by the cyclocondensation of α,α-dibromoaldehydes with 2,4-diamino-6-hydroxypyrimidine under mild basic conditions in good yields. Application of this protocol has been demonstrated in the synthesis of a metabolite of Pemetrexed disodium, a novel multi-targeted antifolate.



The pyrrolopyrimidines are known to have a broad spectrum of biological activities viz. anti-inflammatory,[1] antiviral,[2] antifungal,[3] CNS[4] and antitumor activity[5] including inhibitors of thymidylate synthase (TS), dihydrofolate reductase (DHFR), and Glycinamideribonucleotide formyltransferase (GARFT). Examples of clinically used TS, GARFT, and DHFR inhibitors are pemetrexed (**1**),[6]

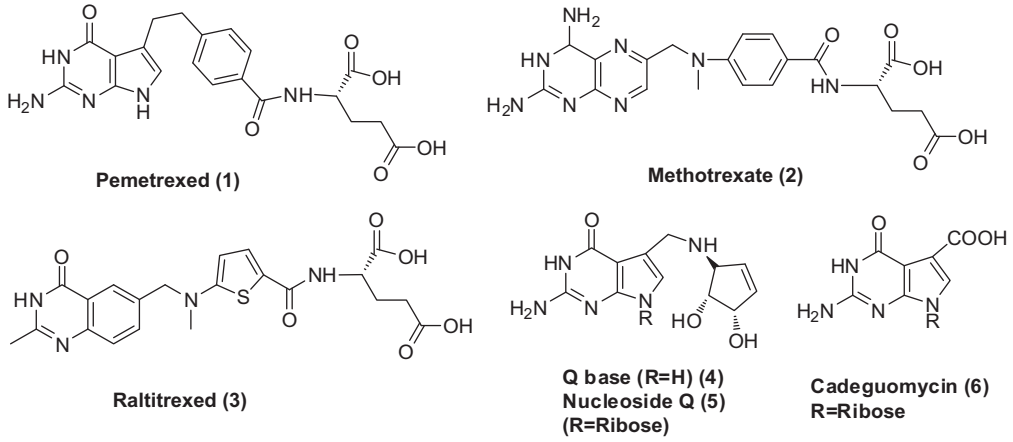


**Figure 1.** Chemical structures of pyrrolopyrimidines and clinically used TS, GARFT, and DHFR inhibitors.

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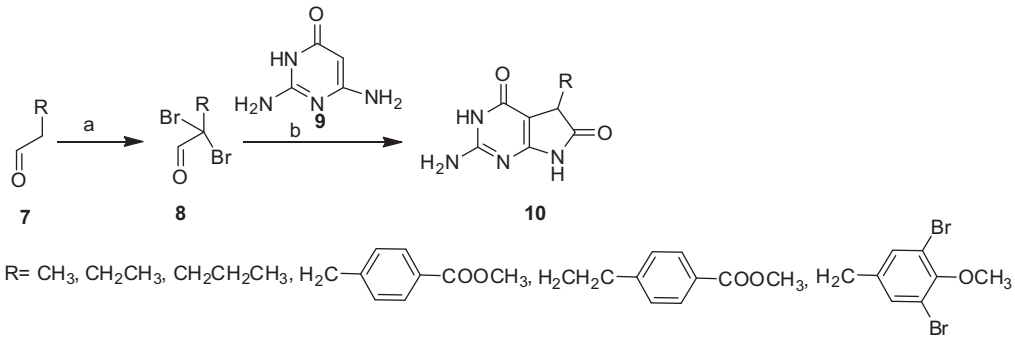
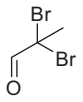
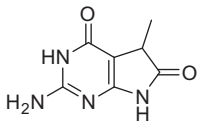
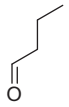
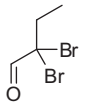
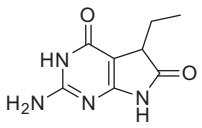
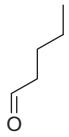
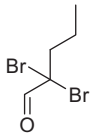
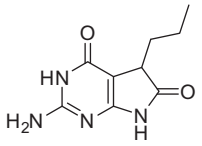
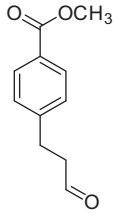
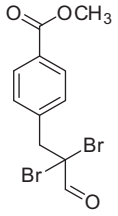
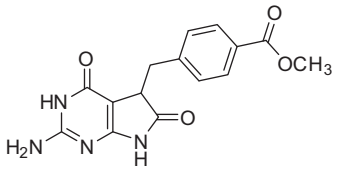
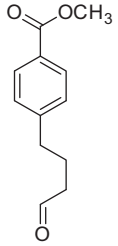
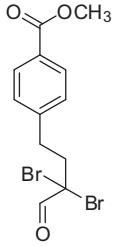
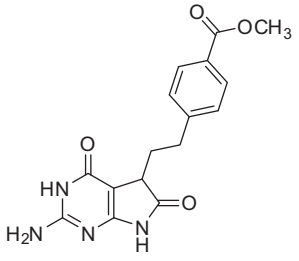
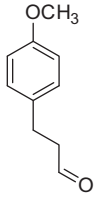
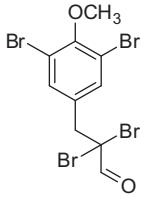
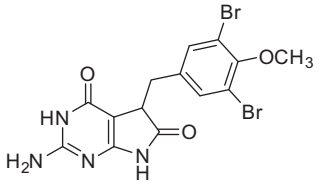


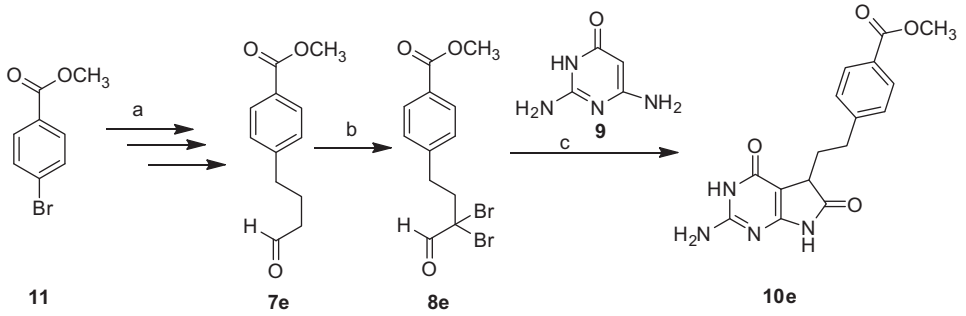

**Scheme 1.** Synthesis of 5-substituted-4,6-dioxo-pyrrolo[2,3-*d*]pyrimidines. Reagents and conditions: (a) Bromine, HBr/AcOH, 25–30 °C, 5–12 h; (b) NaOAc, ACN/Water, 40–45 °C, 3–7 h.

**Table 1**
Condensation of α,α-dibromoaldehyde (**8a**–**8f**) with 2,4-diamino-6-hydroxypyrimidine (**9**)

| Entry | Aldehyde (**7**) | α,α-Dibromo aldehyde (**8**) | Product (**10**) | Yield[a] (%) |
|---|---|---|---|---|
| a |  |  |  | 74 |
| b |  |  |  | 78 |
| c |  |  |  | 76 |
| d |  |  |  | 81 |
| e |  |  |  | 85 |
| f |  |  |  | 84 |

[a] Unoptimized yields calculated from α,α-dibromoaldehyde (**8**).

methotrexate (**2**)[7] and raltitrexed (**3**)[8] which are shown in Figure 1. Also, pyrrolo[2,3-*d*]pyrimidine ring system is a common motif in several natural products and biologically active molecules viz. Q base (**4**), nucleoside Q (**5**), and cadeguomycin (**6**).[9]




**Scheme 2.** Synthesis of key intermediate (**10e**) of metabolite (**15**). Reagents and conditions: (a) (i) 3-Butyn-1-ol, $PdCl_2$, $PPh_3$, CuI, $Et_2NH$, 50 °C, 4 h; (ii) Pd/C, $H_2$, 50 psi, DCM, 3.5 h; (iii) NaOCl, TEMPO, KBr, $NaHCO_3$, DCM, −10 to 0 °C, 1 h; (b) Bromine, HBr/AcOH, DCM, 25–30 °C, 8 h; (c) NaOAc, ACN/Water, 40–45 °C, 5 h.

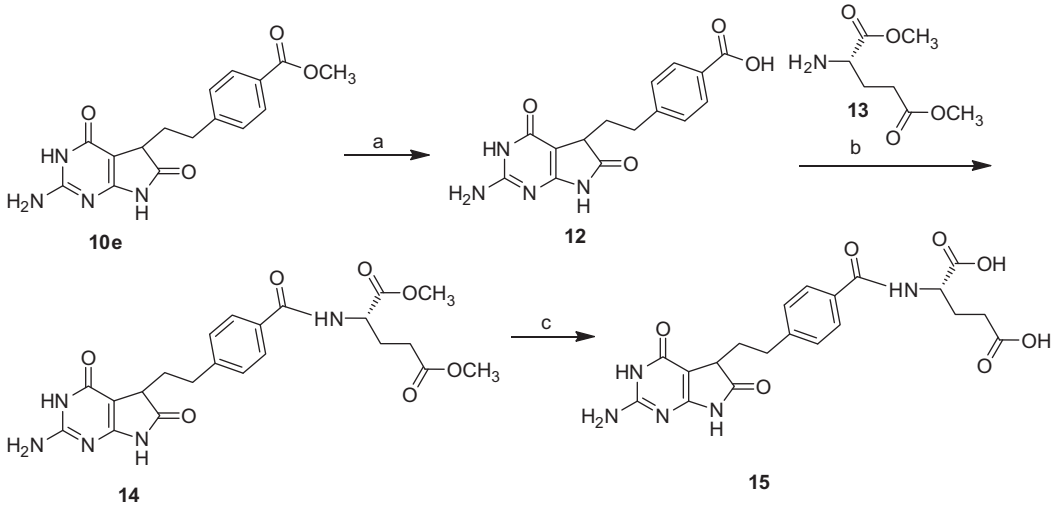
Chemistry of pyrrolopyrimidines is well established[6,10] and several approaches were chosen by medicinal chemists for the synthesis of analogues[6,10,13] to achieve the activity superior to methotrexate (**2**). In this connection several novel pyrrolo[2,3-*d*]pyrimidine compounds as neoplasm inhibitors were developed. A practical synthesis was reported by Taylor et al.[11] involving cyclocondensation of 2,4-diamino-6-hydroxypyrimidine with α-bromoaldehyde to synthesize 5-substituted 4-oxo pyrrolo[2,3-*d*]pyrimidine, which is a key intermediate in the synthesis of pemetrexed (**1**). Alternately, a series of pyrrolopyrimidine containing hetero atom in the side chain were synthesized by cyclocondensation of β-alkoxy and β-amino-α-bromoaldehydes with 2,4-diamino-6-hydroxypyrimidine.[12] However, there is limited literature available for the synthesis of 5-substituted-4,6-dioxo-pyrrolo[2,3-*d*]pyrimidines, which includes long synthetic sequence, low yields, and expensive reagents.[13] Hence, there is a need for an alternate approach to support our ongoing research for the synthesis of 5-substituted-4,6-dioxo-pyrrolo[2,3-*d*]pyrimidine analogues. Herein, we report a short and efficient synthesis for 5-substituted 4,6-dioxo-pyrrolo[2,3-*d*]pyrimidines (**10**) involving condensation of α,α-dibromoaldehyde (**8**) and 2,4-diamino-6-hydroxy pyrimidine (**9**) under mild basic conditions.

Synthesis of 5-substituted-4,6-dioxo-pyrrolo[2,3-*d*]pyrimidine (**10**) involves firstly the preparation of suitably substituted α,α-dibromoaldehyde (**8**). Substituted α,α-dibromoaldehydes were synthesized by treating aldehyde (**7**) with excess bromine (5 equiv) and catalytic hydrobromic acid/acetic acid (0.1 equiv) in dichlormethane.[15] The advantage of the present procedure is that thus generated dibromoaldehydes (**8**) are pure enough to undergo condensation with 2,4-diamino-6-hydroxy pyrimidine (**9**). Thus formed compound **8** was condensed with 2,4-diamino-6-hydroxy-pyrimidine (**9**) (1 equiv) using sodium acetate (2 equiv) in 10 volumes of acetonitrile and water mixture (1:1) to afford 5-substituted-4,6-dioxo-pyrrolo[2,3-*d*]pyrimidine (**10**) in good yields, Scheme 1.[16]

The generality of the above transformation has been demonstrated by the condensation of a variety of α,α-dibromoaldehyde (**8a**–**8f**) and 2,4-diamino-6-hydroxypyrimidine (**9**) compounds with good yields, Table 1, and the variation of substitution in α,α-dibromoaldehyde (**8**) has not shown any significant impact on the progress of the reaction. It was observed that while bromination of 3-(4-methoxy-phenyl) propionaldehyde (**7f**), 2,2-Dibromo-3(3,5-dibromo-4-methoxy-phenyl)-propionaldehyde (**8f**) was obtained as major product, which could be attributed to aromatic bromination on an electron rich aromatic ring.

In continuation of our work, this methodology was applied to the synthesis of a metabolite (**15**)[14] of pemetrexed (**1**). Pemetrexed (**1**) is a multitargeted antifolate and its polyglutamated metabolites were reported as inhibitors of several important folate dependent enzymes including TS, GARFT, and DHFR enzymes.[6]

The metabolite (**15**) can be obtained from the advanced intermediate, 5-substituted-4,6-dioxo-pyrrolopyrimidine (**10e**). The synthesis of compound **10e** can be envisaged from the basic starting material *p*-bromobenzoic acid methyl ester (**11**), Scheme 2. The methyl ester **(11)** could be converted into desired aldehyde (**7e**) using the reported procedures in the literature.[11] Thus obtained




**Scheme 3.** Synthesis of metabolite of Pemetrexed. Reagents and conditions: (a) NaOH, 0–10 °C, 2 h; (b) CDMT, NMM, DMF, 25–30 °C, 4 h; (c) NaOH, ethanol, HCl, 0–5 °C, 1 h.

aldehyde (**7e**) was treated with excess bromine and hydrobromic acid/acetic acid in dichloromethane to afford the corresponding α,α-dibromoaldehyde (**8e**). The dibromoaldehyde (**8e**) was reacted with 2,4-diamino-6-hydroxypyrimidine (**9**) to afford the advanced intermediate (**10e**). Ester (**10e**), thus obtained was hydrolyzed in presence of an alkali to afford acid (**12**) and then coupled with dimethyl L-glutamate ester (**13**) in presence of coupling agent 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) to yield the corresponding protected metabolite (**14**). The ester groups in compound **14** were hydrolyzed in presence of alkali to afford the metabolite (**15**) as shown in Scheme 3.

The structures of 5-substituted 4,6-dioxo-pyrrolo[2,3-*d*]pyrimidines (**10a**–**10f**, **12**, **14** and **15**) were identified by appropriate spectral data.[17] Thus, the structure of **10c** has been elucidated by single crystal X-ray diffraction along with other spectroscopic techniques.[18]

In summary, a new, short and efficient synthetic protocol for the synthesis of 5-substituted-4,6-dioxo-pyrrolo[2,3-*d*]pyrimidines under mild basic conditions was established with good yields from α,α-dibromoaldehyde and 2,4-diamino-6-hydroxypyrimidine. The methodology has been successfully applied to the synthesis of a metabolite of pemetrexed. The structure of one of the compound (**10c**) was elucidated by the single crystal X-ray diffraction.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.141.

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15. *Representative experimental procedure for the synthesis of α,α-dibromoaldehydes* (**8a**–**8f**): To a solution of aldehyde (1 equiv) in dichloromethane (DCM) (20 vol) taken into a round bottomed flask, 33% hydrobromic acid in acetic acid solution (0.1 equiv) was added. The reaction mass was cooled 0–5 °C and then added excess bromine (5 equiv) in dichloromethane slowly at temperature less than 10 °C. After completion of addition, temperature of the reaction mass was raised to 25–30 °C and stirred for 5–12 h. The completion of reaction was confirmed by TLC (Eluent: EtOAc/*n*-hexane, 2:8). The reaction mass was washed with 10% aq sodium thiosulphate (2 × 10 vol), 7% aq sodium bicarbonate (2 × 10 vol) and water (10 vol). The organic layer was separated and evaporated under reduced pressure at 35–40 °C to obtain red to light brown colored title compound (yield: 90–95%).
16. *Representative experimental procedure for the synthesis of 5-substituted-4,6-dioxo-pyrrolo[2,3-d]pyrimidines* (**10a**–**10f**): α,α-Dibromoaldehyde (1 equiv) and 2,4-diamino-6-hydroxy pyrimidine (1 equiv) were taken into round bottomed flask, and acetonitrile (5 vol) was then added followed by water (5 vol). After stirring for 5 min, sodium acetate (2 equiv) was added into the reaction mass. Then the reaction mass was stirred for 3–7 h at 40–45 °C. After monitoring the reaction by TLC (mobile phase: MeOH/DCM, 2:8) for the absence of starting material, the reaction mass was cooled to 25–30 °C. Filtered and washed with 1:1 acetonitrile and water mixture. The solid obtained was dried under vacuum at 45–50 °C to obtain dark tan to light pink colored solid (yield: 74–85%).
17. *2-Amino-5-methyl-5,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-4,6-dione* (**10a**): $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 1.23 (d, 3H, *J* = 7.2 Hz), 3.20 (q, 1H, *J* = 7.2 Hz), 6.66 (br s, 2H, $D_2O$ exchangeable), 10.34 (br s, 1 H, $D_2O$ exchangeable), 10.48 (br s, 1H, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, 400 MHz): δ 14.40, 38.57, 92.06, 157.09, 157.79, 163.82, 180.64. HRMS calcd for $C_7H_9N_4O_2$ $(M+H)^+$: 181.0726, found: 181.0724. IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3389, 2926, 1743, 1719, 1681, 1533, 1502, 1450, 1352, 1248, 1170, 777.
*2-Amino-5-ethyl-5,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-4,6-dione* (**10b**): $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 0.77 (t, 3H, *J* = 7.2 Hz), 1.71–1.88 (m, 2H), 3.24 (t, 1H, *J* = 5.6 Hz), 6.68 (br s, 2H, $D_2O$ exchangeable), 10.40 (br s, 1H, $D_2O$ exchangeable), 10.48 (br s, 1H, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, 400 MHz): 9.67, 21.67, 44.77, 89.74, 157.22, 157.85, 164.59, 179.85. HRMS calcd for $C_8H_{11}N_4O_2$ $(M+H)^+$: 195.0882, found: 195.0881. IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3417, 2964, 1737, 1721, 1650, 1519, 1431, 1343, 1284, 1166, 771.
*2-Amino-5-propyl-5,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-4,6-dione* (**10c**): $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 0.83 (t, 3H, *J* = 7.2 Hz), 1.20–1.35 (m, 2H), 1.63–1.81 (m, 2H), 3.24 (t, 1H, *J* = 5.6 Hz), 6.65 (br s, 2H, $D_2O$ exchangeable), 10.33 (br s, 1H, $D_2O$ exchangeable), 10.48 (br s, 1H, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, 400 MHz): δ 14.04, 18.58, 31.12, 43.70, 90.45, 157.15, 157.83, 164.34, 180.23. HRMS calcd for $C_9H_{13}N_4O_2$ $(M+H)^+$: 209.1039, found: 209.1037. IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3404, 2958, 1715, 1659, 1524, 1431, 1349, 1274, 1165, 783. X-ray crystallographic data for **10c**: $C_{10}H_{16}N_4O_3$, M = 240.26, monoclinic, space group *C*2/*c*, *a* = 34.30(4) Å, *b* = 4.994(4) Å, *c* = 27.38(3) Å, β = 148.791(6)°, *V* = 2430(4) Å$^3$, *T* = 298 K, Z = 8, $D_c$ = 1.314 g/$cm^{-1}$, μ(Mo-Kα) = 0.7107 Å, 13,170 reflections measured, 2509 unique reflections, 673 observed reflections [$I > 2.0\sigma(I)$], R1_obs = 0.091, *w*R2_all = 0.155, Gof = 1.264.
*4-(2-Amino-4,6-dioxo-4,5,6,7-tetrahydro-3H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-benzoic acid methyl ester* (**10d**): $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 3.14–3.25 (m, 2 H), 3.65 (t, 1H, *J* = 4.0 Hz), 3.80 (s, 3H), 6.63 (br s, 2H, $D_2O$ exchangeable), 7.17 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 2H, *J* = 8.4 Hz), 10.35 (br s, 1H, $D_2O$ exchangeable), 10.42 (br s, 1H, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, 400 MHz): δ 33.33,

44.88, 51.95, 88.87, 127.65, 128.60, 129.50, 143.32, 157.18, 158.02, 164.27, 166.10, 178.77. HRMS calcd for $C_{15}H_{15}N_4O_4$ $(M+H)^+$: 315.1093, found: 315.1108. IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3454, 2954, 1743, 1724, 1707, 1666, 1514, 1432, 1355, 1294, 1118, 779.

*4-[2-(2-Amino-4,6-dioxo-4,5,6,7-tetrahydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-ethyl]-benzoic acid methyl ester* (**10e**): $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 2.0–2.09 (m, 2H), 2.72–2.78 (m, 2H), 3.30 (t, 1H, $J$ = 6.0 Hz), 3.83 (s, 3H), 6.70 (br s, 2H, $D_2O$ exchangeable), 7.33 (d, 2H, $J$ = 8.0 Hz), 7.86 (d, 2H, $J$ = 8.0 Hz), 10.37 (br s, 1H, $D_2O$ exchangeable), 10.56 (br s, 1H, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, 400 MHz): $\delta$ 30.73, 31.68, 43.44, 52.01, 90.37, 127.26, 128.72, 129.23, 147.69, 157.30, 158.08, 164.61, 166.24, 179.75. HRMS calcd for $C_{16}H_{17}N_4O_4$ $(M+H)^+$: 329.1250, found: 329.1260. IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3410, 2924, 1721, 1703, 1658, 1532, 1438, 1390, 1293, 1116, 762.

*2-Amino-5-(3,5-dibromo-4-methoxy-benzyl)-5,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-4,6-dione* (**10f**): $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 3.07 (dd, 2H, $J$ = 4.8, 9.6 Hz), 3.63 (t, 1H, $J$ = 4.0 Hz), 3.73 (s, 3H), 6.70 (br s, 2H, $D_2O$ exchangeable), 7.27 (s, 2H), 10.35 (br s, 1H, $D_2O$ exchangeable), 10.42 (br s, 1H, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, 400 MHz): 31.90, 44.76, 60.31, 88.59, 116.51, 133.32, 137.06, 151.65, 157.30, 158.08, 164.38, 178.72. HRMS calcd for $C_{14}H_{13}Br_2N_4O_3$ $(M+H)^+$: 442.9354, found: 442.9370. IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3395, 2929, 1732, 1717, 1650, 1526, 1473, 1427, 1260, 1151, 777.

*4-[2-(2-Amino-4,6-dioxo-4,5,6,7-tetrahydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-ethyl]-benzoic acid* (**12**): $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 1.91–2.13 (m, 2H), 2.67–2.80 (m, 2H), 3.30 (t, 1H, $J$ = 6.0 Hz), 6.76 (br s, 2H, $D_2O$ exchangeable) 7.30 (d, 2H, $J$ = 8.0 Hz), 7.83 (d, 2H, $J$ = 8.0 Hz), 10.39 (br s, 1H, $D_2O$ exchangeable), 10.55 (br s, 1H, $D_2O$ exchangeable), 12.73 (br s, 1H, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, 400 MHz): $\delta$ 30.81, 31.63, 43.43, 90.33, 128.51, 128.59, 129.39, 147.09, 157.32, 158.07, 164.58, 167.40, 179.73. HRMS calcd for $C_{15}H_{15}N_4O_4$ $(M+H)^+$: 315.1093, found: 315.1096. IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3366, 2938, 1751, 1692, 1658, 1582, 1525, 1433, 1381, 1256, 1177, 759.

*2-{4-[2-(2-Amino-4,6-dioxo-4,5,6,7-tetrahydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-ethyl]-benzoylamino}-pentanedioic acid dimethyl ester* (**14**): $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 1.98–2.06 (m, 2 H), 2.07–2.13 (m, 2 H), 2.44 (t, 2 H $J$ = 7.6 Hz), 2.69–2.76 (m, 2H), 3.30 (t, 1H, $J$ = 6.0 Hz), 3.58 (s, 3H), 3.64 (s, 3H), 4.43–4.48 (m, 1H), 6.73 (br s, 2H, $D_2O$ exchangeable), 7.29 (d, 2H, $J$ = 8.0 Hz), 7.78 (d, 2H, $J$ = 8.0 Hz), 8.66 (d, 1H, $J$ = 7.6 Hz, $D_2O$ exchangeable), 10.42 (br s, 1H, $D_2O$ exchangeable), 10.58 (br s, 1H, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, 400 MHz): $\delta$ 25.79, 30.00, 30.98, 31.52, 43.43, 51.42, 51.98, 51.98, 90.33, 127.56, 128.25, 131.20, 145.73, 157.28, 158.05, 164.59, 166.59, 172.27, 172.70, 179.74. HRMS calcd for $C_{22}H_{26}N_5O_7$ $(M+H)^+$: 472.1832, found: 472.1829. IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3330, 2924, 1735, 1649, 1655, 1586, 1523, 1436, 1352, 1261, 1166, 774.

*2-{4-[2-(2-Amino-4,6-dioxo-4,5,6,7-tetrahydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-ethyl]-benzoylamino}-pentanedioic acid* (**15**): $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$1.91–2.02 (m, 2H), 2.04–2.08 (m, 2H), 2.34 (t, 2H, $J$ = 7.6 Hz), 2.65–2.77 (m, 2H), 3.43 (t, 1H, $J$ = 6.8 Hz), 4.34–4.40 (m, 1H), 6.93 (br s, 2H, $D_2O$ exchangeable), 7.28 (d, 2H, $J$ = 8.0 Hz), 7.78 (d, 2H, $J$ = 8.4 Hz), 8.47 (d, 1H, $J$ = 7.6 Hz, $D_2O$ exchangeable), 10.44 (br s, 1H, $D_2O$ exchangeable), 10.57 (br s, 1H, $D_2O$ exchangeable), 12.1–13.0 (br, 2H, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, 400 MHz): $\delta$ 26.15, 30.61, 30.98, 31.43, 43.42, 52.13, 90.13, 127.52, 128.21, 131.60, 145.54, 157.62, 157.99, 164.51, 166.39, 173.61, 174.03, 179.78. HRMS calcd for $C_{20}H_{22}N_5O_7$ $(M+H)^+$: 444.1519, found 444.1519. IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3434, 2930, 1714, 1652, 1645, 1586, 1529, 1435, 1353, 1260, 1167, 768.

18. 100 mg of compound **10c** was dissolved in 12 mL of *N,N*-dimethylformamide and methanol solvent mixture (1:3 v/v), and single crystals of **10c** were obtained after 15 days (refer Supplementary data).
Crystallographic data (excluding structure factors) for the structures in this paper has been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication number, CCDC 817007 for **10c**. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.